Teratogenic Effects of 'Recreational' Drugs

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SUMMARY

Published data from clinical studies for commonly abused substances were identified through a TOXLINE bibliographic search. References in teratology monographs and review articles were also used. Emphasis was placed on controlled epidemiological studies. Available evidence suggests that maternal alcohol or cocaine abuse substantially increases the risk of congenital anomalies among infants. Many recreational drugs cause neurobehavioral dysfunction in neonates exposed before birth.

RÉSUMÉ

La recherche littéraire "TOXLINE" a permis d'identifier les données publiées à partir d'études cliniques concernant les substances qui sont couramment l'objet d'abus. Les références citées dans les monographies traitant de tératologie et les articles de révision ont aussi été utilisés. On a mis l'emphase sur les études épidémiologiques contrôlées même si, dans certains cas, nous avons aussi considéré les séries cliniques. Les données disponibles suggèrent que l'alcoolisme maternel ou l'abus de cocaïne chez la mère augmente substantiellement le risque de malformations congénitales chez les enfants. De nombreuses drogues récréatives sont cause de dysfonction neurocomportementale chez les nouveau-nés exposés avant la naissance.

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SUBSTANCE ABUSE occurs throughout our society and is associated with many serious social and medical problems. The use of "recreational" drugs by young women also raises concern about the potential teratogenic effects of these agents. In many cases, women stop using such drugs once pregnancy is recognized, but this is usually well into the period during which teratogenic risk is greatest. In other instances, abuse continues throughout pregnancy, particularly in women who are addicted.

It is well known that maternal exposure to some drugs can interfere with normal development of the embryo. The nature of the effect depends on the innate susceptibility of the embryo or fetus, the mother's metabolism, the chemical and pharmacological nature of the agent, the dose, and the time of gestation during which exposure takes place.

Exposure to teratogens before implantation generally has an "all-or-none" effect, ie, the embryo is either resistant to irreparable damage by the agent or fails to implant because of damage produced by the exposure.[1] Susceptibility to structural malformations is usually greatest during embryogenesis (about 2 to 10 weeks after conception). Some teratogens are capable of inhibiting cell growth or proliferation at any point in gestation. Because the central nervous system (CNS) continues to develop throughout gestation, the CNS remains vulnerable to teratogenic effects much later than other parts of the body.

Alteration of CNS development is often associated with neurobehavioral deficits.[2] Such deficits can occur in the absence of gross structural malformations of the brain and do not become manifest until long after birth.[3] Recreational drugs are taken primarily for their effects on the CNS, so these agents are of particular concern as possible behavioral teratogens.

Methodological limitations of clinical studies investigating the teratogenicity of commonly abused drugs hamper attempts to determine the risks associated with substance abuse during pregnancy. Most clinical studies are hospital-based and therefore include subjects who are not typical of pregnant women who use recreational drugs. Clinical studies usually rely on self-reports to determine the frequency and amount of drug use; the validity of such reports is often highly questionable, given the present sociopolitical climate.

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The very nature of drug abusers' lifestyles complicates interpretation of recreational drug teratogenicity studies. For example, many drug addicts have a low socio-economic status and do not have proper nutrition or prenatal care. Substance abuse can predispose a woman to additional health risks associated with AIDS, other venereal disease, or violence.

Drug use is usually not confined to a single substance; most abusers use alcohol and tobacco as well.[4,5] Combinations of drugs are used to augment or offset the pharmacological effects of one another. In addition, street drugs often contain a host of contaminants, and less expensive agents are substituted for more expensive drugs on the street. Tolerance to drugs of abuse can lead to an increase in the amount used, which in turn increases the risk of toxicity.

Thus, it is difficult to determine whether adverse effects noted among the children of women who have abused drugs during pregnancy result from the agents themselves or other associated factors. These confounding factors can be controlled in animal teratology studies, but experimental conditions often bear little resemblance to the circumstances of human substance abuse, making extrapolation to humans even more difficult than is usual with animal experiments.[6]

The purpose of this paper is to review human studies that address the effects of substance abuse during pregnancy. Published data for each drug of abuse were identified through a TOXLINE bibliographic search (1965 to 1990). References provided in the *Catalog of Teratogenic Agents,*[7] *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk,*[8] *Chemically Induced Birth Defects,*[9] and selected review articles were also used.

Emphasis was placed on epidemiological studies because these studies provide the only means of obtaining quantitative estimates of the strength and statistical significance of associations between drug exposures in pregnant women and abnormalities in their infants. Clinical series were also considered in this review, although the lack of control groups necessitates caution when interpreting data from these studies.

Alcohol

Alcohol is a CNS depressant that is widely consumed in beverages for its intoxicating effect. A pattern of congenital anomalies, called the fetal alcohol syndrome, occurs among infants born to women who abuse alcohol chronically and in large amounts during pregnancy.[10,11] Typical fetal alcohol syndrome is usually seen among the children of women who drink more (and often much more) than 90 mL of absolute alcohol daily throughout pregnancy. This is the equivalent of about six beers, six glasses of wine, or six mixed drinks daily. Characteristic features of the fetal alcohol syndrome include prenatal and postnatal growth deficiency, mental retardation, behavioral disturbances, and typical facial appearance. The latter consists of short palpebral fissures, hypoplastic midface, hypoplastic philtrum, and thin upper lip vermilion. Congenital heart disease and brain malformations are common, but other serious malformations are less frequent.

Fetal alcohol syndrome occurs in 30% to 40% of women who drink heavily during pregnancy. Lower levels of maternal alcohol consumption during pregnancy have been associated with a variety of less severe but persistent manifestations in children.[12-16] Among the children of women who drink an average of more than 30 to 60 mL of absolute alcohol daily during pregnancy (the equivalent of about two to four beers, glasses of wine, or mixed drinks), minor anomalies, growth deficiency, intellectual deficits, and behavioral abnormalities seem to occur with increased frequency. Maternal alcohol use during pregnancy has also been associated with an increased risk of miscarriage and stillbirth.

No safe level for maternal drinking during pregnancy has been established. The risks of maternal episodic ("binge") drinking have not been clearly defined, but could be substantial.[16] Transient withdrawal symptoms, such as tremors, hypertonia, and irritability, have been observed among infants born to women who chronically drank alcohol late in pregnancy.[17,18]

Tobacco

Many studies of the reproductive effects of cigarette smoking have been performed. Extensive reviews are available on this subject.[19-21] Well-controlled studies involving thousands of women have generally shown that the frequency of spontaneous abortion

is 20% to 80% higher than expected among women who smoke cigarettes during pregnancy.[19,21] The risks appear to be greater for heavy smokers than for light smokers. Perinatal mortality also seems to be somewhat increased among the infants of women who smoke cigarettes during pregnancy.

Dozens of studies involving well over 100 000 pregnancies have examined the association between maternal cigarette smoking and birth weight.[19,21,22] Low birth weight is unequivocally associated with maternal smoking in proportion to the dose. This effect seems to be due primarily to fetal growth retardation rather than to prematurity. Controversy exists over whether the low birth weight seen among the infants of women who smoke is caused by the smoking or by other correlated factors. The preponderance of evidence favors the former view.

The relationship of maternal smoking and congenital anomalies has been examined in several epidemiological studies involving thousands of children.[21,22] In general, no association between the frequency of major congenital anomalies and maternal smoking has been observed. A few studies have found associations between maternal smoking and various congenital anomalies, but such associations have generally been weak and not reproducible in other investigations.

Marijuana

Marijuana is derived from the plant *Cannabis sativa* and is one of the most widely abused recreational drugs. It is usually smoked as cigarettes (called reefers or joints) or eaten. Published epidemiological studies of malformations among the infants of women who smoked marijuana during pregnancy do not distinguish first trimester from later gestational exposure. Moreover, estimates of the magnitude and duration of exposure in these investigations is absent or very crude.

In one cohort study of 1246 pregnancies in which the mother smoked marijuana, the frequency of major malformations in the offspring was no greater than expected.[23] A similar result was obtained when only the offspring of 137 women who smoked marijuana daily were considered. Five infants with intrauterine growth retardation and minor dysmorphic features have been reported whose mothers smoked two to 14 joints of marijuana daily during pregnancy.[24] The prevalence of this exposure in the general population and the non-specificity of the anomalies in the infants preclude any causal inference. The frequency of minor anomalies was no greater than expected among 25 children of women who smoked marijuana during pregnancy in another study.[25] Birth weight and length do not appear to be associated with maternal marijuana smoking during pregnancy in most well-controlled studies,[23,26,27] although a few investigations have found such an association.[28,29] An increased frequency of abnormal neonatal behaviors has also been observed among the children of 291 women who used marijuana during pregnancy, but no such abnormalities were noted in some of these children who were tested at 1 year of age.[30]

Barbiturates

No information is available on the teratogenic effects of maternal barbiturate abuse, although considerable data exist on the effects of therapeutic use of phenobarbital as an anticonvulsant or sedative. The frequencies of congenital anomalies in general, of major malformations, of minor anomalies, and of main classes of congenital anomalies were no greater than expected among the children of 1415 women treated with phenobarbital during the first 4 lunar months of pregnancy in the Collaborative Perinatal Project.[31] Similarly, there was no increase in the frequency of congenital anomalies among the children of 8037 women treated with phenobarbital at any time during pregnancy in this study. The frequency of congenital anomalies appears to be somewhat increased among the children of women who take phenobarbital during pregnancy for treatment of seizure disorder rather than for some other reason.[32-35] This effect sometimes is not seen when cases in which phenobarbital exposure has occurred without concomitant exposure to other anticonvulsants are analyzed separately.[34-36]

One interpretation of these data is that the increased frequency of malformations observed is due to teratogenic effects of factors associated with seizures per se rather than to a specific effect of phenobarbital.[37]

Chronic maternal use of phenobarbital late in pregnancy has been associated with transient neonatal sedation or withdrawal symptoms in the infants.[38,39] Features seen in these newborns include hyperactivity, irritability, and tremors. In the Collaborative Perinatal Project,[32] the adjusted intelligence quotient at age 4 years was no different in children exposed to phenobarbital during gestation than in unexposed children.

Benzodiazepines

Diazepam is the most widely used and abused benzodiazepine, but other tranquilizers of this group are also abused. Available epidemiological data regarding the risk of malformations among children born to women who took diazepam during pregnancy are inconsistent. The frequency of congenital anomalies was not increased among the infants of more than 150 women who took diazepam during the first trimester of pregnancy in two cohorts of the Boston Collaborative Drug Surveillance Program[40,41] or among the infants of 60 women treated with diazepam in a French study.[42] In contrast, maternal use of diazepam during the first trimester of pregnancy was almost three times as frequent among the mothers of 1427 children with congenital anomalies as among controls in one study,[43] but not in another involving 417 children with multiple congenital anomalies.[44] The suggestion that there exists a "benzodiazepine embryofetopathy" comprised of typical facial features, neurological dysfunction, and other anomalies[45] is not generally accepted.

Maternal use of diazepam or other benzodiazepines during the first trimester of pregnancy was found significantly more often among the mothers of 599,[46] 111,[47] and 49[48] children with oral clefts in three case-control studies. No such association was seen in four other case-control studies that involved 194,[49] 611,[50] 522,[44] and 1201[44] children with oral clefts. Similarly, the frequency of oral clefts was not increased among the children of 854 women who took diazepam during the first trimester of pregnancy in a large cohort study.[51] Considering these data as a whole, it seems likely that, if the risk for cleft lip or palate in the child of a woman who takes diazepam early in pregnancy is increased at all, this risk is considerably less than 1%.

Two case-control studies involving 383[33] and 390[43] children with cardiovascular malformations have suggested an association with maternal use of diazepam or related drugs during the first trimester of pregnancy. However, Bracken[52] reanalyzed the data from his study and failed to find a significant association, and Zierler and Rothman[53] reported that no association was found in a follow-up study of another 298 children with congenital heart disease. If there is an increased risk of congenital heart disease among the children of women who take diazepam during the first trimester of pregnancy, this risk is probably no more than 1% to 2%.

Treatment of the mother with diazepam during the third trimester of pregnancy or during delivery has resulted in apnea, hypotonia, and hypothermia in the newborn.[54,55] Tremors, irritability, and hypertonia reminiscent of neonatal narcotic withdrawal occur in some babies born to mothers chronically treated with diazepam in the third trimester.[56] The effect, if any, of prenatal exposure of diazepam on CNS function in later childhood or adulthood is unknown.

Phencyclidine

Phencyclidine is widely used as a "recreational" drug. It can be combined with marijuana (called "super grass" or "clickers") or cocaine ("space basing").[57,58] No malformations were noted in a series of 94 infants of women who abused phencyclidine during their pregnancies.[59] In another series of 57 infants whose mothers used phencyclidine during pregnancy, two of the children looked "morphologically abnormal," but no recognizable or consistent pattern of congenital anomalies was found.[60] One of the children in this series exhibited severe developmental delay. The cause of these abnormalities is unknown, and no direct relationship to the maternal use of phencyclidine has been established.

Alterations of neonatal neurological function and behavior have frequently been observed among the children of women who abused phencyclidine during pregnancy.[59-62] The abnormalities seen include symptoms resembling narcotic withdrawal (jitteriness, abnormal suck, irritability), alterations of tone, abnormal eye move-

ments, sudden outbursts of agitation, and rapid changes in the level of consciousness. Lower than expected weight, length, and head circumference have also been noted among these infants.[60]

Stimulants

Cocaine. Cocaine is a CNS stimulant that is widely used and abused recreationally.[63,64] Other substances are frequently substituted for cocaine or mixed with it in samples obtained on the street.[65,66] With the emergence of "crack," a smokable and relatively inexpensive form of cocaine, the abuse of cocaine has increased dramatically. Thirteen of 32 full-term infants born to women with documented cocaine use during pregnancy were found to have disruptive brain anomalies on cranial ultrasound examination in one study.[67] Similar brain lesions have been noted among infants of women who used cocaine during pregnancy in other series.[68-70] These reports are of great concern because cerebral infarction has been observed after cocaine exposure in children and adults.[71]

A number of children born to mothers who abused cocaine during pregnancy have been found to have congenital anomalies of the type thought to be due to vascular disruption. These include at least five infants with segmental intestinal atresia and nine with limb reduction defects.[72-74] Such anomalies could be due to the vasoconstrictive and hypertensive actions of cocaine.

An association between maternal cocaine use during pregnancy and the occurrence of congenital anomalies of the genitourinary system in the infants has been reported in some small studies,[73,75,76] but not others.[77-79] Two of the latter studies found increased frequencies of congenital anomalies in general among the children of women who used cocaine chronically during pregnancy.[78,79] It is difficult to determine an overall risk of congenital anomalies related to maternal cocaine use during pregnancy because there appears to be a systematic publication bias in favor of studies that show such an association and against studies that do not.[80] Growth retardation involving weight, length, and head circumference has consistently been noted among infants born to women who abused cocaine during pregnancy.[77,78,81-84]

Amphetamines. Both amphetamine and methamphetamine are common drugs of abuse. Methamphetamine is used illicitly to "cut" or dilute other drugs. A smokable form of methamphetamine called "ice" is becoming more widespread among drug users.[85] Most street samples sold as amphetamines contain as little as 1% amphetamines; such drugs as phencyclidine, benzocaine, and lidocaine are often substituted.[86] The frequency of congenital anomalies was no greater than expected among the children of 367 women who were treated with dextroamphetamine or the children of 89 women treated with methamphetamine during the first 4 lunar months of pregnancy in the Collaborative Perinatal Project.[31]

Similarly, no association was observed with congenital anomalies in other cohort studies involving 52 children born to mothers who took dextroamphetamine or 347 children born to mothers who took some drug in the amphetamine group early in pregnancy.[87,88] The frequency of congenital anomalies was not increased among the children of 1069 women who took dextroamphetamine, of 320 women who took methamphetamine, or of 1694 children of women who took a drug of the amphetamine class any time during pregnancy.[31,88] The results of case-control studies have been less consistent. Use of dextroamphetamine during early pregnancy was found more frequently than expected among the mothers of 458 infants with a variety of congenital anomalies[89] and among the mothers of 184 children with cardiovascular malformations.[90]

A history of maternal dextroamphetamine use during the period of fetal bile duct formation was observed with unusually high frequency among 11 infants with primary biliary atresia.[91] The clinical importance of these observations is brought into question by their inconsistency with cohort studies. A significant decrease in body weight, length, and head circumference was observed in one cohort study of 52 women who abused methamphetamines throughout pregnancy.[92] Seventy-three percent of these women used other substances in addition to methamphetamine during their pregnancy, however.

Opiates and opioids

Heroin. It has been estimated that as

many as 300 000 women are addicted to heroin in the United States.[4] Adulterants are frequently found in street samples of heroin. The frequency of malformations does not appear unusually high in most cohorts and clinical series of infants born to heroin-addicted mothers.[93-96] A statistically significant increase in the frequency of malformations was observed in one study of 830 infants born to narcotic-dependent mothers,[97] but the frequency of malformations in children born to addicts in this study was about what would be expected in general (2.4%), while the frequency in control infants was inexplicably low (0.5%).

Although several anecdotal reports of children with congenital anomalies born to mothers addicted to heroin have been published, no consistent pattern of malformations has been observed,[98] and no causal inference is possible. Intrauterine growth retardation, perinatal death, and a variety of other perinatal complications have frequently been observed in the offspring of narcotic-addicted mothers,[96,99,100] but it is unclear whether these effects are due to fetal exposure to heroin or to the generally poor health of these mothers. Subsequent growth of these children appears to be normal in most cases, although head circumference can continue to be somewhat smaller than expected.[101,102]

Mild developmental delay or behavioral disturbances are often observed in the children of women addicted to narcotics.[102,103] Neonatal withdrawal symptoms are observed in 40% to 80% of infants born to heroin-addicted women.[96,104,105] Withdrawal symptoms include tremors, irritability, sneezing, vomiting, fever, diarrhea, and occasionally seizures. Although the duration of these symptoms is sometimes prolonged, it is usually less than 3 weeks.

Meperidine. No studies regarding the effects of meperidine abuse during pregnancy have been reported, but data regarding the infants of women treated with this drug therapeutically are available. The frequency of congenital anomalies was no greater than expected among the infants of 268 women who were treated with meperidine during the first 4 lunar months of pregnancy or of 1100 women who were treated with the drug at any time during pregnancy in the Collaborative Perinatal Project.[31] Similarly, maternal use of meperidine during the first trimester of pregnancy was not associated with congenital anomalies in more than 50 infants in another cohort study.[40] Maternal treatment with meperidine within a few hours of delivery can cause transient respiratory depression in newborn infants.[106] Behavioral alterations have also been observed among such infants in the newborn period,[107,108] but no physical or psychological deficit was apparent at age 5 to 10 years in one series of 70 children born to mothers treated with meperidine within 2 hours of birth.[109]

Pentazocine. No congenital anomalies were observed among the infants of 51 female drug abusers who used a pentazocine and tripelennamine combination (T's and Blues) at various times during pregnancy.[110] Lower than expected birth weight, length, and head circumference have been noted among infants born to women who abused pentazocine and tripelennamine during pregnancy.[110,111] Transient neonatal withdrawal symptoms occur in infants born to women who take pentazocine chronically late in pregnancy.[110-112] The infants' symptoms resemble those seen in neonatal withdrawal from other narcotics: irritability, hyperactivity, vomiting, and high-pitched cry.

Propoxyphene. The frequencies of congenital anomalies in general, of major malformations, of minor anomalies, and of major classes of congenital anomalies were no greater than expected among the children of 686 women who took propoxyphene during the first 4 lunar months of pregnancy in the Collaborative Perinatal Project.[31] Similar findings were reported in another cohort study involving more than 100 pregnancies exposed to propoxyphene during the first trimester.[40] The frequency of congenital anomalies was no greater than expected among the infants of 2914 women who took propoxyphene at any time during pregnancy in the Collaborative Perinatal Project.[31] Transient neonatal withdrawal symptoms have been reported in infants born to mothers who took propoxyphene chronically during pregnancy.[113,114] Irritability, hyperactivity, tremors, and high-pitched cry are the usual clinical features.

Lysergide

Lysergide (LSD) has powerful hallucinogenic effects, for which it is used recreationally. The drug is used in many forms: powder, tablet, capsule, sugar cubes or tattoos, or blotting paper. Street samples are often adulterated, and substitutes are sometimes sold as LSD.

Several case reports have been published describing children with a variety of congenital anomalies born to mothers who used lysergide before or during pregnancy.[115,116] No consistent pattern of anomalies is apparent among these children, and many of them have anomalies or syndromes that are likely to have a cause unrelated to the mother's use of lysergide. Abnormalities of the limbs were noted most often among affected children, but the type of abnormality varied greatly, and this probably represents a reporting bias.

No satisfactory epidemiological study of congenital anomalies among infants born to women who used lysergide during pregnancy has been published. In one series of 86 pregnancies in women who used lysergide at unspecified times during gestation, eight children were born with various congenital anomalies.[117] Five of these children had CNS defects, but only two were exposed to lysergide during the first trimester. The available data provide no convincing evidence that a mother's use of lysergide during pregnancy increases the risk of malformations in her children.

Conclusion

Maternal alcohol or cocaine abuse during pregnancy can substantially increase the risk of congenital anomalies among infants. Other commonly abused drugs have not been established as frequent causes of serious structural anomalies among infants exposed before birth. Almost all of these drugs have been found to produce neurobehavioral alterations in early infancy. Little is known about the teratogenic and perinatal effects when recreational drugs are used only occasionally during pregnancy.

In general, the safest recommendation is for women to refrain from all recreational drug use during the entire gestational period, although withdrawal from narcotic agents during pregnancy can be dangerous.[4] More research on the long-term neurodevelopmental and behavioral effects of prenatal exposure to recreational drugs is needed in view of the enormous financial and social costs that rehabilitation and education of these children can ultimately have. ■

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